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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/444,284	11/19/1999	RONALD VOGELS	4231US	8464

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EXAMINER
CHEN, SHIN LIN

ART UNIT	PAPER NUMBER
1632	14

DATE MAILED: 05/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/444,284	VOGELS ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover she t with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14,16-21,24-26,28-32 and 37-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14,16-21,24-26,28-32 and 37-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed 2-28-02 has been entered. Claims 1, 4, 19, 20, 24-26, 28-32, 37, 44, 47, 49, 52 and 58 have been amended. Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 are pending and under consideration.

Double Patenting

1. Applicant is advised that should claim 5 be found allowable, claims 6-8 and 41 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See M.E.P.. § 706.03(k). The limitations recited in claims 6-8 and 41 are already required in claim 1, from which claim 5 depends.

Claim Objections

2. Claim 10 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 10 fails to further limit claim 5, from which it depends. A dependent claim must include all limitations of preceding claims, and claim 10 excludes protein fragments from adenovirus subgroup B as required by preceding claims.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 2, 25, 37-40 and 42 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention and is repeated for the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). Applicant's arguments filed 2-28-02 have been fully considered but they are not persuasive.

Applicants argue that Example 2, page 37 and Table II, page 47 of the specification indicate what "significantly" means and the value for chimeric adenovirus was compared to a control so that one of skill in the art can understand the scope of the term "significantly" (amendment, p. 9-10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). Example 2 and Table II only disclose the difference between the value of chimeric adenovirus and wild type adenovirus 5. It is still unclear to what extent of the difference between the value of chimeric adenovirus and wild type adenovirus 5 would be considered "significantly". Whether the value of 142 (Fib 12) in Table II is considered significantly reduced as compared to 254 (control Ad5) and whether 315 (Fib 12) in Table II is considered significantly reduced as compared to 428 (control Ad5). One of skilled

in the art would not be able to determine what is "significantly" reduced and what is not "significantly" reduced.

5. Claim 37 remains rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See M.E.P.. § 2172.01 and is repeated for the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). Applicant's arguments filed 2-28-02 have been fully considered but they are not persuasive.

Applicants amend the claim to read on "incorporating a fragment of a fiber protein" of adenovirus 16 in an adenovirus capsid thereof, and argue that one of ordinary skill would know how to do it (amendment, p. 12). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). It is still unclear what reduce tissue tropism of the adenovirus capsid and whether the use of fiber protein of adenovirus 16 would reduce the tissue tropism for liver cells.

6. Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants' amendment filed 2-28-02 necessitates this new ground of rejection.

The phrase "said protein fragments are not from an adenovirus of subgroup B and are from an adenovirus of subgroup C" is vague and renders the claim indefinite. Claim 1 is directed

to a gene delivery vehicle comprising a tissue tropism determining fragment of a **subgroup B adenovirus fiber protein**, and claim 10 depends on claim 1. It is unclear how the gene delivery vehicle of claim 10 comprises protein fragments of subgroup C adenovirus but not that of subgroup B adenovirus. The conflict between the limitations make it unclear what claim 10 is directed to.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 2, 38-40, 44, 45, 51, 52 and 54-57 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention and is repeated for the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). Applicant's arguments filed 2-28-02 have been fully considered but they are not persuasive.

Applicants argue that the specification provides example of gene delivery vehicle exhibiting a tropism for SMC, increased tropism for endothelial cells, and reduced tissue tropism for liver cells. Applicants further argue that the specification describes methods, sequences, and genetic maps for the claimed invention, and as long as at least one method for making and using

the claimed invention is enabled, then the enablement requirement of 35 U.S.C. 112 is satisfied (amendment, p. 12-13). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). It should be noted that this is a written description rejection under 35 U.S.C. 112 first paragraph but not an enablement rejection under 35 U.S.C. 112 first paragraph. The scope of the claimed invention is very broad, and the few examples provided in the specification are not sufficient to represent the full scope of the invention claimed. The specification fails to provide the structural features of a tropism-determining protein from different adenoviruses, non-adenoviruses, or non-virus delivery vehicles. Structural features that could distinguish compounds in the genus from others in the polypeptide class are missing from the disclosure. No common structural attributes identify the members of the genus. This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the gene delivery vehicles as they are broadly claimed.

9. Claims 1, 2, 4-14, 16-21, 24-26, 28-32 and 37-58 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for adenovirus fiber 16 chimera that infects HUVEC endothelial cells or smooth muscle cells significantly better than the control adenovirus type 5 *in vitro* and none of the disclosed fiber chimeras are targeted specifically to liver and spleen *in vivo*, does not reasonably provide enablement for any gene delivery vehicle comprising at least a tissue tropism for smooth muscle cells, increased tropism for endothelial

cells, or with a significantly reduced tissue tropism for liver cells for *in vitro* or *in vivo* gene delivery other than the *in vitro* use of adenoviruses encoding the disclosed fiber protein chimeras, for a cell comprising said gene delivery vehicle, a pharmaceutical composition comprising said gene delivery vehicle, a method of delivering nucleic acid to smooth muscle cells by using any adenovirus capsid *in vivo*, and a method of significantly reducing an adenovirus capsid of a tissue tropism for a liver cells by using fiber protein of adenovirus 16 in an adenovirus capsid *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). Applicant's arguments filed 2-28-02 have been fully considered but they are not persuasive.

Applicants argue that if one use is enabled then the application is enabling for the claimed invention and the *in vitro* example is correlated to *in vivo* use such that the *in vivo* use is enabled (amendment, p. 13-14). Applicants further argue that the cited references (Rudinger and Kaye et al.) do not disclose the differences between *in vitro* and *in vivo* uptake of a chimeric virus by cells (amendment, p. 14). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). The specification must provide sufficient enabling disclosure for the claimed invention. The *in vitro* environment, which can be controlled, differ dramatically from the *in vivo* environment, which is much more complicated and has various uncontrolled factors that will affect the result *in vivo*. As discussed in preceding Official action, the art of gene therapy or gene delivery *in vivo* was unpredictable at the time of

the invention, the result of *in vitro* experiment can not be extrapolated to successful gene delivery or gene therapy *in vivo*.

The cited references (Rudinger and Kaye et al.) are to point out that it was unpredictable for the protein function from mere amino acid sequence. It would be unpredictable whether various altered tropism-determining proteins, chimeric proteins having protein fragments from a virus or at least two different viruses, such as fragments of virus capsid proteins, could provide a tissue tropism for SMC, increased tropism for endothelial cells, or reduced tissue tropism for liver cells *in vitro* or *in vivo*.

10. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants' amendment filed 2-28-02 necessitates this new ground of rejection.

Claim 10 is directed a gene delivery vehicle comprising virus capsid protein fragments from at least two different viruses and said fragments are from subgroup C adenovirus but not from subgroup B adenovirus.

The specification only discloses generation of recombinant adenovirus chimera having protein fragments from subgroups B and C but fail to provide sufficient description and support for the generation of recombinant adenovirus chimera having protein fragments from only

subgroup C. Further, applicants' amendment filed 2-28-02 fails to point out whether and where the specification has support for the amendment made in claim 10. Thus, the subject matter of claim 10 is considered new matter.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1, 4-8, 11-14, 16, 17, 19, 24 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Stevenson et al., 1997 (Journal of Virology, Vol. 71, No. 6, p. 4782-4790). This is to reinstate the 35 U.S.C. 102(b) rejection recited in the Official action mailed 4-11-01 (Paper No. 9, see page 11-13).

The subject matter of the claims and the teachings of Stevenson are as discussed in the Official action mailed 4-11-01 (Paper No. 9, see page 11-13).

Applicants amended claim 1 to read on a gene delivery vehicle comprising a tissue tropism determining fragment of a subgroup B adenovirus fiber protein and said tissue tropism is for **smooth muscle cells**.

Applicants argument in the amendment filed 7-16-01 (Paper No. 10, see page 10) is that Stevenson fails to disclose a gene delivery system with the ability to transduce smooth muscle

cells. This is not found persuasive because the claims are product claims, and Stevenson teaches every structural elements as recited in the claims. The recombinant adenoviral chimeras taught by Stevenson would inherently have the ability to transduce smooth muscle cells, i.e. have the tropism for smooth muscle cells. The specification of the present application indicates that "Clearly fiber 16 and fiber 11 are better suited for infection of SMC than fiber 35 and fiber 51. Nevertheless, all subgroup B fiber mutants tested infect SMC better as compared to Ad5" (see page 42, lines 27-30). Further, Su et al, 2001 (Journal of Vascular Research, Vol. 38, p. 471-478) discloses an adenoviral vector, Av9LacZ, that encodes beta-galactosidase and contains a chimeric fiber protein, 5T3H which has Ad3 fiber protein, that redirects viral vector binding to the Ad3 adenoviral receptor. Su also discloses that the adenoviral vector can transduce rabbit, pig, monkey and human smooth muscle cells, and it transduces human smooth muscle cells with much higher efficiency. In view of the disclosure of the specification and Su, the recombinant adenoviral chimeras taught by Stevenson would inherently have the ability to transduce smooth muscle cells, and thus, claims 1, 4-8, 11-14, 16, 17, 19, 24 and 41 are anticipated by Stevenson.

13. Claims 1, 4-8, 10-14, 16, 17, 19, 24 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Wickham et al., 1998 (US Patent No. 5,770,442). Applicants' amendment on claim 10 necessitates this new ground of rejection. With respect to the claims other than claim 10, the teachings of Wickham is the same as disclosed by Stevenson as set forth above in the

preceding 102(b) rejection. The inclusion of the claims other than claim 10 is for the sake of the completeness of this rejection.

Claim 10 is directed to a gene delivery vehicle comprising tissue tropism determining fragments of capsid from at least two different viruses that are not subgroup B but are subgroup C adenovirus, and said tissue tropism is for smooth muscle cells.

Wickham teaches generation of an Ad2-Ad5 adenoviral chimera that changes adenoviral antigenicity without changing receptor specificity by replacing the native Ad5 receptor binding domain with the nonnative Ad2 receptor binding domain (e.g. example 1, column 11, 12). The recombinant adenoviral chimeras taught by Wickham would inherently have the ability to transduce smooth muscle cells, i.e. have the tropism for smooth muscle cells, because like Ad5 as discussed in the preceding 102(b) rejection section, Ad2 will transduce smooth muscle cells. Thus, claim 10 is anticipated by Wickham.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 1, 4-14, 17-19, 24, 26 and 43 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wickham et al., 1997 (Journal of Virology, Vol. 71, No. 11, p. 8221-8229) in view of Stevenson et al., 1997 (Journal of Virology, Vol. 71, No. 6, p. 4782-4790) and Woo et al., 1997 (US Patent No. 5,631,236) and is repeated for the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). Applicant's arguments filed 2-28-02 have been fully considered but they are not persuasive.

Applicants argue that Wickham does not teach or suggest using capsid fragments from two different adenoviruses and Stevenson does not teach or suggest a chimeric adenovirus with a tropism for SMC. Applicants further argue that Woo does not teach or suggest a recombinant adenoviral vector with a tropism for SMC (amendment, p. 16-17). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 9-28-01 (Paper No. 11). Wickham teaches generation of adenovirus containing modifications to the Ad fiber coat protein, which in fact is a part of capsid, that change its tropism, and said modification increased gene delivery to endothelial and SMC. Wickham suggests alteration of the natural tropism of adenovirus will permit gene transfer into specific cell types and greatly broaden the scope of

target diseases via Ad, and demonstrates the feasibility of tissue-specific receptor targeting in cells which express low levels of Ad fiber receptor.

Stevenson teaches preparation of a chimeric fiber cDNA having Ad3 (subgroups B) fiber head domain fused to the Ad5 (subgroup C) fiber tail and shaft incorporated into the genome of an adenovirus vector to generate a recombinant adenoviruses containing the chimeric fiber protein. Stevenson suggests that "exchange of fiber head domain is a viable approach to the production of adenovirus vectors with cell-type specific transduction properties" and may "extend this approach to the use of ligands for a range of different cellular receptors in order to target gene transfer to specific cell types at the level of transduction". The teachings of Stevenson would provide motivation for one of ordinary skill to substitute DNA encoding the modified Ad fiber protein as taught by Wickham with the chimeric fiber cDNA having Ad3 (subgroups B) fiber head domain fused to the Ad5 (subgroup C) fiber tail and shaft as taught by Stevenson for the tropism of SMC. In fact, Wickham also teaches delivering nucleic acid to SMC via administering to SMC an adenovirus containing modified fiber coat protein, which in fact is a part of capsid. Although Wickham, Stevenson, and Woo alone does not teach all the element of the claimed invention, it would be obvious for one of ordinary skill at the time of the invention to practice the claimed invention according to the collective teachings of Wickham, Stevenson and Woo because of the reasons discussed above.

Conclusion

No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See M.E.P.. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Scott Priebe can be reached on (703) 308-7310. The fax phone number for this group is (703) 308-4242.

Questions of formal matters can be directed to the patent analyst, Patsy Zimmerman, whose telephone number is (703) 305-2758.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Shin-Lin Chen, Ph.D.